In accordance with 37 CFR § 1.121(c), attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Version With Markings to Show Changes Made".

REMARKS

Applicants have canceled claims 2, 19, 21, and 23-26. Applicants have amended claims 1, 3, 7-18, 20, and 22 to address the issues raised by the Examiner and to more clearly express the inventive concept. Support for the term "DNA-dependent" added to claims 20 and 22 can be found at page 12, line 11 of the specification. Applicants have further introduced new claims 27 and 28. New claim 27 is directed to the embodiment wherein the recombinant Sendai viral vector comprises a mutant Sendai virus ("having at least one gene encoding Sendai viral protein selected from the group consisting of NP, P, and L proteins, is deleted or altered"). Support for this claim is found in the specification as originally filed, particularly at pages 8-10 and 15, lines 9-11. New claim 28 is directed to the embodiment wherein the recombinant Sendai viral vector comprises a foreign gene inserted prior to the ORF of the NP gene. Support for this claim can be found at page 26, line 5. Thus, at present, claims 1-28 are pending in the application. Applicants submit that no new matter has been added.

Applicants respectfully submit that the rejections and objections set forth in the Office Action mailed October 18, 2002 are moot in view of the amendments presented herein. Accordingly, Applicants respectfully request that the Examiner reconsider the outstanding objections and rejections in the in light of the amendments and remarks herein:

Double Patenting Rejections

M.P.E.P. 706.02(k) states that where two applications of different inventive entities are co-pending and the filing dates differ, a provisional rejection should be made in the later filed application if the applications have a common assignee or a common inventor. Where the applications are claiming the same patentable invention, a terminal disclaimer may be used to overcome a rejection in a common ownership situation if the earlier filed application has matured

into a patent.

In this case, all the cited applications were filed after the present application. Accordingly, provisional rejections should not be made in this application, only in the later filed applications. Moreover, submission of a terminal disclaimer is only appropriate when the earlier filed application (i.e., the present application) has matured into a patent. Thus, Applicants respectfully submit that the provisional rejections of the pending claims as obvious in view of the claims of Application Nos. 09/702,498 and 09/823,699 should be withdrawn.

Regarding the provisional rejection of the claims as obvious in view of the claims of Application No. 09/436,504, Applicants submit that this application is not commonly assigned and therefore, cannot be avoided through the filing of a terminal disclaimer. The noted application is merely a later filed application having one common inventor, not the same inventive entity. While it is appropriate to reject the claims of the '504 application as being obvious in view of the present claims, it is not appropriate to reject the present claims on such grounds since the '504 application, were it to issue as a patent, would not constitute "prior art" to the present application.

Rejections Under 35 U.S.C. 112, Second Paragraph

The Examiner rejected claims 1-26 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claims the invention. Specifically:

(i) the definition of the term "disseminative" is unclear;

(ii) the intended scope of claim 1, as being distinct from wild type viral mutants, is unclear;

(iii) the term "reconstituted" in claim 13 lacks antecedent basis;

(iv) the scope of claims 18 and 19 is unclear;

(v) the scope of claims 20-25 is unclear; and

(vi) the term "said host" in claim 26 lacks antecedent basis.

With regard to item (i), Applicants have deleted the term "disseminative" from all claims.

With regard to items(ii), Applicants have canceled description of the noted embodiment from claim 1 and put them in new independent claim 27. With regard to new claim 27, Applicants have

expressly defined the mutation as comprising a deletion or alteration of a gene encoding one of the NP, P, and L proteins. Applicants respectfully submit that the scope of this claim is clear and unambiguous. Moreover, such a mutant is distinct in terms of both structure and function from those mutants arising in nature or isolated by classical methods, such as the defective interfering (DI) particles of the prior art which are deficient in most of the viral genes.[1]

With regards to item (iii), Applicants have deleted the term "reconstituted" from claim 13.

With regards to item (iv), Applicants have canceled claim 19 and amended claim 18 to depend from method claim 10.

With regard to item (v), Applicants have canceled claims 21 and 23-25 and amended claims 20 and 22 to refer to the cell as not expressing "heterologous DNA-dependent RNA polymerase". In host cells expressing Sendai viral proteins NP, P, and L, genes encoding these proteins are integrated in the chromosome of the host cells and therefore these proteins are expressed using RNA polymerase inherent in the cells. When cDNA encoding recombinant Sendai viral RNA is directly introduced into the host cells, RNA polymerase that transcribes said RNA with said DNA as a template is necessary to produce Sendai viral vectors of the present invention. Such RNA polymerase may be DNA-dependent RNA polymerase that is heterologous to the host cells as described at page 12, lines 10-12 of the instant specification.

In contrast, when recombinant Sendai viral RNA is transcribed *in vitro* and said RNA is introduced into host cells, the host cells do not require RNA polymerase for transcribing said RNA. This embodiment is described in pending claims 20 and 22. Therefore, "heterologous RNA polymerase" referred to in claims 20 and 22 does not refer to the Sendai viral RNA polymerase that is RNA-dependent and an expression product of Sendai viral NP, P, and L genes, but DNA-dependent RNA polymerase necessary to transcribe recombinant Sendai viral RNA from cDNA encoding said RNA.

In this connection, two kinds of host cells are described in the claims - one is for producing (reconstituting) the Sendai viral vector as referred to in claims 6-10, 18-20 and 22 and

[1] DI particles are described at page 11, line 16 of the instant specification as well as at p. 1198 of Bernard Fields' book "Virology" (1996), a copy of which is provided herewith.

the other is for producing a foreign protein as referred to in claims 11 and 12. To more clearly define the claimed invention, Applicants have amended the claims to refer to the former is recited as "cells" and the latter is recited as "host cells".

With regard to item (vi), Applicants have canceled claim 26.

Accordingly, Applicants respectfully submit that claims 1-28 meet the requirements of 35 U.S.C. § 112, second paragraph.

Rejections Under 35 U.S.C. 112, First Paragraph

Written Description/ New Matter:

The Examiner rejected claims 14-17, 19, and 26 under 35 U.S.C. § 112, first paragraph, as containing subject matter that was not described in the specification. To expedite prosecution, Applicants have canceled claims 19 and 26. Furthermore, Applicants have canceled the limitations of claim 14 directed to intergenic and downstream insertion sites. Accordingly, the rejection is now moot.

Regarding support for claim 15 (directed to a recombinant Sendai viral vector in which NP, P, or L is deleted or modified), the Examiner's attention is directed to pages 8-10, and 13, wherein the deletion, inactivation, or modification of one or more viral genes encoding viral functional proteins is described. In particular, at page 13, line 21, Applicants state that any genome gene may be deleted or modified. In this context, the term "modification" encompasses many alterations, including changes such as substitution, addition, insertion, and deletion. In fact, the specification discloses at the last paragraph of page 12 that "if cells which express all viral proteins (N, P, and L) required for the initial transcription, replication, and encapsidation are constituted, the recombinant Sendai virus can be produced entirely without using helper viruses such as vaccinia virus." This means that the recombinant Sendai virus does not necessarily need to express N, P, and L proteins. From these descriptions, it is clear that the instant specification provides support for the claimed embodiments.

Enablement:

The Examiner rejected claims 1-26 under 35 U.S.C. § 112, first paragraph because the specification "while being enabling for a Sendai virus with a foreign gene inserted before the NP ORF does not reasonably provide enablement for the full scope of 'disseminative' viruses." Specifically, "the specification does not teach deletions or alterations which result in self-propagating virus, and does not teach trans-complementation of defective Sendai genomes with defects in replication or packaging genes".

Applicants submit that the amendments presented herein render the Examiner's enablement concerns moot. In particular, Applicants have canceled the term "disseminative" from the claim. Moreover, regarding the issue of foreign gene insertion sites, Applicants respectfully submit that one skilled in the art could make a Sendai virus with a foreign gene inserted at the other site than before the NP ORF without undue experimentation, as is the test for enablement. Specifically, since the Sendai virus genome contains only six genes, the number of possible insertion sites that are not within a Sendai viral gene is seven. The amount of experimentation needed to assay these seven possible sites does not rise to the level of "undue experimentation". In fact, one of ordinary skill in the art could readily determine which of these seven insertion sites allow for appropriate expression of a foreign gene using routine experimentation.

Furthermore, Applicants submit that operable foreign gene insertion sites could not only be readily identified by those skilled in the art and but could further be routinely assessed and assayed for expression simply by following the guidance of the present specification, taken in conjunction with the teachings and instructions of the prior art. Moreover, successful intergenic insertions (and others) are described in the article by Tokusumi et al. (Virus Research (2002) 86:33-38), a copy of which is provided with the supplemental IDS submitted previously; see specifically Figures 1 and 2. All of the SeV plasmids studied by Tokusumi et al. provided both uninterrupted expression of Sendai viral proteins and measurable expression of the inserted foreign gene (e.g., SEAP, beta-galactosidase). Thus, Tokusumi et al. confirm Applicants' contention - that foreign gene insertion need not affect expression of the Sendai viral proteins and that measurable foreign gene expression by a recombinant Sendai viral vector is not restricted to a single insertion site. In fact, Tokusumi et

al. demonstrate that a number of operable insertion sites exist within Sendai viral genome. Accordingly, it is clear that foreign gene expression may occur at insertion sites other than the NP ORF site described in the Examples of the present specification.

In conclusion, Applicants submit that claims 1-28 are enabled by the accompanying specification and, therefore, meet the enablement requirement of 35 U.S.C. § 112, first paragraph. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection under section 112, first paragraph.

Priority

The Examiner has denied Applicants the benefit of the priority applications on the grounds that the prior applications do not provide an adequate written description of the claimed subject matter. Specifically, with regards to the JP application, the Examiner submits that the application conveys only a desire to obtain disseminative Sendai viruses with gene modifications or foreign gene insertions, but does not convey actual possession of any desired modified viruses. Regarding the PCT application, while the Examiner admits that the disclosure confirms reduction to practice of the foreign gene embodiment, it does not disclose where in the genome these foreign genes were inserted. The Examiner thus concludes that the effective filing date of the present application is December 1, 2000.

Applicants respectfully traverse this conclusion. First, the Examiner has ignored the fact that the present application is a continuation of U.S. Application Serial No. 09/071,591 filed May 1, 1998. Thus, even if Applicants are denied their foreign priority claims, the effective filing date of the present application is May 1, 1998 and not December 1, 2000 as suggested by the Examiner.

Regarding the denial of Applicants' foreign priority claims, Applicants respectfully submit that the presently claimed invention (i.e., modified Sendai viruses) is fully described and enabled by the earlier filed applications. The test for sufficiency of support in a parent application is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." *Ralston Purina Co. v. Far-Mar-Co. Inc.*, 772 F.2d 1570, 1575, 227 U.S.P.Q. 177, 179 (Fed. Cir. 1985) (quoting *In re Kaslow*, 707 F.2d

1366, 1375, 217 U.S.P.Q. 1089, 1096 (Fed. Cir. 1983). Moreover, the MPEP further states that the "subject matter of the claim need not be described literally (i.e., using the same terms or *in haec verba*) in order for the disclosure to satisfy the description requirement." MPEP 2163.03; see also *In re Lukach*, 440 F.2d 1263, 169 U.S.P.Q. 795 (C.C.P.A. 1971). Instead, *Staehelin v. Secher*, 24 U.S.P.Q.2d 1513, (Bd. Pat. App. & Int. 1992) states that the inquiry is whether one following applicant's specification would necessarily select the later claimed subject matter. *Freerksen v. Gass*, 21 U.S.P.Q.2d 2007 (B.P.A.I. 1990). The question, therefore, is whether the originally filed application would have conveyed to a person of ordinary skill in the art that applicants invented the subject matter later claimed by them including the limitations in question. *In re Smythe*, 480 F.2d 1376, 178 U.S.P.Q. 279 (C.C.P.A. 1973).

Herein, the priority applications and the instant US application mainly differ in the disclosure of working examples. However, as the presence of working examples is not a statutory requirement, the omission of such should not be deemed fatal. *In re Borkowski*, 154 U.S.P.Q. 643 (C.C.P.A. 1970), *In re Rainer*, 146 U.S.P.Q. 218 (C.C.P.A. 1965). Importantly, all the applications describe the first efficient reconstitution of Sendai virus from cDNA and the use of such reconstituted viruses as vectors for foreign gene expression. Prior to Applicants' invention, a reconstitution system for Sendai virus had not been established. The "written description requirement may be satisfied if the broader concept 'would naturally occur to one skilled in the art' upon reading the earlier specification." *Levi Strauss & Co. v. Golden Trade, S.R.L.*, 1991 WL 710822 (S.D.N.Y. Dec. 1, 1995) (quoting *In re Smythe*, 480 F.2d 1376, 1384 (C.C.P.A. 1973); *Waldemar Link, GmbH & Co. v. Ostoenics Corp.*, 32 F.3d 556, 558 (Fed. Cir. 1994)). In the instant case, once the process for viral reconstitution is known, the steps required to insert a foreign gene or modify a desired viral gene are readily apparent to those skilled in the art; the construction of foreign gene carrying Sendai virus from a reconstituted virus involves merely routine experimentation. In fact, it is well accepted that an applicant preferably omits from a patent specification description of that which is well known in the art. Moreover, that which is inherent need not be expressly described. See *Kennecott Corp. v. Kyocera Int'l, Inc.*, 835 F.2d 1419, 5 U.S.P.Q.2d 1194 (Fed. Cir. 1987), *cert. denied*, 486 U.S. 1008 (1988). Thus, an actual reduction to practice of an embodiment of the claimed invention is not

required to meet enablement or to demonstrate possession.

Accordingly, Applicants respectfully submit that the priority applications meet the requirements of 35 USC § 112, first paragraph. Thus, the presently claimed invention is entitled to the benefit of the earlier filing dates.

Rejections Under 35 U.S.C. 102

Kato:

The Examiner rejected claims 1-13 under 35 U.S.C. § 102(b) for being anticipated by Kato et al. (Genes to Cells, June 1996). The Examiner cited specifically pages 573-574.

Applicants respectfully submit that the claim amendments presented herein render these rejections moot. However, in the event that the Examiner feels that they are applicable to the newly presented claims, Applicants submit the following comments:

In order to qualify as "prior art" under 35 USC 102(b), a reference's publication date must be more than one year prior to Applicant's filing date. The present application has an effective US filing date of May 1, 1998. Moreover, as discussed above, the pending claims are entitled to the benefit of an earlier priority date, namely the filing dates of PCT Application PCT/JP96/03069 (filed October 22, 1996) and Japanese Application No. 07-285,417 (filed November 1, 1995). Thus, the relevant date for prior art purposes is November 1, 1995. Since the Kato et al. article was published in June of 1996, it cannot qualify as "prior art" to the present application under any section of 35 U.S.C. § 102, much less 35 U.S.C. § 102(b) which requires publication one year prior to filing. Thus, Applicants respectfully submit that the article to Kato et al. is not "prior art" to the present invention and is therefore irrelevant to the patentability of pending claims 1-27. Accordingly, Applicants respectfully request reconsideration and withdrawal of the above rejection under section 102(b).

Furthermore, in order to anticipate a claim, a single reference must disclose each and every element of the claimed invention. In this case, Kato et al. do not disclose a recombinant Sendai viral vector containing a genome carrying a foreign gene as is required by amended claim 1; nor do they disclose a method of making same (claim 10) or a method of using same to produce foreign

proteins (claim 11). Rather, the Kato disclosure is limited to the production of a recombinant Sendai virus having a mutation in the *Bam*HI-*Hpa*I segment of the F gene. Accordingly, Kato et al. cannot anticipate claims 1-13 as amended herein.

Hasan, Sakai, or Toriyoshi:

The Examiner rejected claims 1-14, 16-19, 25, and 26 under 35 U.S.C. § 102(b) for being anticipated by Hasan et al. (J. Gen. Virol., November 1997), Sakai et al. (FEBS Letter, 1999) or Toriyoshi et al. (Aids Res. & Human Retroviruses, 1999). The Examiner cited specifically pages 573-574.

In order to qualify as "prior art" under 35 USC 102(b), a reference's publication date must be more than one year prior to Applicant's filing date. The present application has an effective US filing date of May 1, 1998. Therefore, Sakai and Toriyoshi, which have publication dates in 1999, are clearly not "prior art" to the present application. Thus, rejection of the claims thereunder should be withdrawn.

Regarding the Hasan reference, Hasan et al. was published in November of 1997, which is less than one year prior to Applicants' U.S. filing date of May 1, 1998. Therefore, Hasan is clearly not "prior art" under section 102(b). Moreover, as discussed above, the pending claims are entitled to the benefit of an earlier priority date, namely the filing dates of PCT Application PCT/JP96/03069 (filed October 22, 1996) and Japanese Application No. 07-285,417 (filed November 1, 1995). Thus, the relevant date for prior art purposes is November 1, 1995. Since the Hasan et al. article was published in November of 1997, it cannot qualify as "prior art" to the present application under any section of 35 U.S.C. § 102, much less 35 U.S.C. § 102(b) which requires publication one year prior to filing. Thus, Applicants respectfully submit that the article to Hasan et al. is not "prior art" to the present invention and is therefore irrelevant to the patentability of pending claims 1-27. Accordingly, Applicants respectfully request reconsideration and withdrawal of the above rejection under section 102(b).

Conclusion

In sum, Applicants submit that the response herein fully addresses rejections set forth in the outstanding Office Action. Applicants submit that claims 1-28 presented herein are in condition for allowance and respectfully petition for an early notice of allowance. If the Examiner believes a conference would expedite prosecution, he is invited to contact the undersigned.

The previous Office Action set forth a three-month period for response, response being due on or before **January 18, 2003**. Applicants submit herewith a three-month extension of time, extending the deadline for response from **January 18, 2003** to on or before **April 18. 2003**. Accordingly, Applicants submit that this response is timely and no additional fee is required. However, in the event that additional fees are required, the Commissioner is authorized to charge such fees to our Deposit Account No. 50-2101.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the claims:

1. (Currently Amended) A recombinant Sendai viral vector containing a genome ~~having~~ carrying a foreign gene ~~inserted, or a Sendai viral gene deleted or altered, wherein said viral vector retains the disseminative capability of wild-type Sendai virus~~.

2. (Canceled) ~~The recombinant Sendai viral vector of claim 1, wherein one or more genes encoding viral functional proteins is altered~~.

3. (Currently Amended) The recombinant Sendai viral vector of claim ~~2~~1, wherein the recombinant Sendai virus carries a foreign gene capable of being expressed in host cells.

4. (Previously Amended) An RNA molecule comprising RNA contained in the recombinant Sendai viral vector of claim 1.

5. (Previously Amended) An RNA molecule comprising cRNAs of RNAs contained in the recombinant Sendai viral vector of claim 1.

6. (Previously Amended) A kit comprising:
   a. a DNA molecule containing a template cDNA capable of transcribing RNA of claim 4 or 5, and
   b. a unit capable of transcribing said RNA with said DNA as template *in vitro* or intracellularly.

7. (Currently Amended) A kit comprising:
   a. a ~~host~~ cell expressing Sendai viral proteins NP, P, and L, and
   b. the RNA molecule of claim 4 or 5.

8. (Currently Amended) A method for producing the recombinant~~, disseminative~~ Sendai viral vector of claim 1, comprising transfecting RNA of claim 4 or 5 to a ~~host~~ cell wherein the ~~host~~ cell expresses Sendai viral proteins NP, P, and L.

9. (Currently Amended) A kit consisting of the following three components:
   a. a ~~host~~ cell expressing Sendai viral proteins NP, P, and L;
   b. a DNA molecule containing a template cDNA capable of transcribing RNA or cRNA of claim 4 or 5; and
   c. a unit capable of transcribing said RNA with said DNA as template *in vitro* or intracellularly.

10. (Currently Amended) A method for producing the recombinant~~, disseminative~~ Sendai viral vector of claim 1, wherein said method comprises introducing into a ~~host~~ cell expressing Sendai viral proteins NP, P, and L a DNA molecule containing a template cDNA capable of transcribing RNA of claim 4 or 5, and a unit capable of transcribing said RNA with said DNA as a template ~~*in vitro* or~~ intracellularly.

11. (Currently Amended) A method for producing a foreign protein, comprising a process of infecting a host cell with the recombinant~~, disseminative~~ Sendai viral vector of Claim 3, and recovering the expressed foreign proteins.

12. (Currently Amended) A cell culture medium or allantoic fluid containing expressed foreign proteins and Sendai virus particles or parts thereof, obtainable by:
   a. initially transfecting the recombinant~~, disseminative~~ Sendai viral vector of claim 3 to a first host cell, wherein said foreign gene integrated therein encodes a foreign protein;
   b. allowing said recombinant~~, disseminative~~ Sendai viral vector to disseminate to other host cells in the cell culture medium or around the

allantoic fluid following said initial transfection of said recombinant~~, disseminative~~ Sendai viral vector into said host cells;

c. allowing said host cells to express said foreign protein; and

d. recovering said culture medium or allantoic fluid.

13. (Currently Amended) A DNA molecule for expressing a protein encoded by a foreign DNA integrated into a Sendai viral vector DNA, said Sendai viral vector DNA comprising:

a. a promoter;

b. a cDNA encoding an RNA molecule corresponding to the ~~reconstituted~~ Sendai viral genome of claim 1; and

c. DNA encoding a foreign DNA, wherein said foreign DNA is integrated within said Sendai viral genome and the Sendai viral genome containing said foreign DNA is inserted downstream of said promoter in an orientation for transcribing an antisense RNA of both said Sendai viral genome and said foreign DNA.

14. (Currently Amended) The recombinant~~, disseminative~~ Sendai viral vector of claim 1, wherein said ~~foreign gene is inserted (a) prior to a first viral gene within said Sendai viral genome, (b) between a pair of adjacent viral genes within said Sendai viral genome, or (c) after a final viral gene within said Sendai viral genome, in a manner that~~vector allows for the expression in a host cell of both Sendai viral genes contained within said Sendai viral genome and said foreign gene.

15. (Currently Amended) The recombinant~~, disseminative~~ Sendai viral vector of claim 14, wherein at least one gene encoding Sendai viral protein selected from the group consisting of NP, P, and L proteins, is deleted or ~~altered~~modified.

16. (Currently Amended) An RNA molecule comprising RNA contained in the recombinant~~, disseminative~~ Sendai viral vector of claim 14.

17. (Currently Amended) An RNA molecule comprising a cRNA of RNA contained in the recombinant~~, disseminative~~ Sendai viral vector of claim 14.

18. (Currently Amended) The ~~recombinant Sendai viral vector of claim 1~~method of claim 10, wherein said virus is produced entirely without the use of a helper virus.

19. (Canceled) ~~The recombinant Sendai viral vector of claim 14, wherein said virus is produced entirely without the use of a helper virus~~.

20. (Currently Amended) The kit of claim 7, wherein said ~~host~~ cell does not express heterologous DNA-dependent RNA polymerase.

21. (Canceled) ~~The kit of claim 9, wherein said host does not express heterologous RNA polymerase~~.

22. (Currently Amended) The method of claim 8, wherein said cell ~~host~~ does not express heterologous DNA-dependent RNA polymerase.

23. (Canceled) ~~The method of claim 10, wherein said host does not express heterologous RNA polymerase~~.

24. (Canceled) ~~The method of claim 11, wherein said host does not express heterologous RNA polymerase~~.

25. (Canceled) ~~The cell culture medium of claim 12, wherein said first host cell does not express heterologous RNA polymerase~~.

26. (Canceled) ~~The viral vector of claim 14, wherein said host does not express heterologous RNA polymerase~~.

27. (New) A recombinant Sendai viral vector containing a genome in which at least one gene encoding a Sendai viral protein selected from the group consisting of NP, P, and L proteins, is deleted or modified.

28. (New) The recombinant Sendai viral vector of claim 1, wherein said foreign gene is inserted prior to the ORF of the NP gene.